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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09 368,670	08/05/1999	MONTSELTINAS-BRUNET	13 063-2-C2	5801

23703 7590 03/11/2003

BOEHRINGER INGELHEIM CORPORATION
900 RIDGEBURY ROAD
P O BOX 368
RIDGEFIELD, CT 06877

EXAMINER

LUKTON, DAVID

ART UNIT	PAPER NUMBER
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2683

DATE MAILED 03/11/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/368,670

Applicant(s)

LLINAS-BRUNET ET AL.

Examiner

David Lukton

Art Unit

1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 03 January 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-28,30-35,37-88,96 and 99-115 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-28,30-35,37-88,96 and 99-115 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s): _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

Pursuant to the directives of paper No. 15 (filed 12/31/01), claims 1, 26, 30, 40, 45, 67, 78, 86, 96, 99 have been amended, claims 89-92, 97, 98 cancelled, and claims 103-115 added. Subsequently, paper No. 21 (filed 10/11/02) directed amendments to each of claims 27, 47 and 68. Claims 1-28, 30-35, 37-88, 96, 99-115 are now pending.

Claims 1-28, 30-35, 37-88, 96, 99-115 are examined in this Office action.

Applicants' arguments filed 12/21/01 have been considered and found persuasive in part. The rejection of claims 96-99 under 35 U.S.C. 112, first paragraph is withdrawn.

✱

Claims 1-28, 30-35, 37-88, 96, 99-115 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- In claim 1, fourth line from last, the following is recited:

"wherein Het is a five... including aromatic".

Use of the term "including" in this way can be said to leave the metes and bounds undefined. What is suggested is the deletion of the term "including aromatic" from claim 1, and the addition of a new claim such as the following:

The compound according to claim 1 wherein each of R_{12} and R_{12a} is "Het", wherein "Het" is a five, six or seven- membered aromatic heterocycle containing from one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and wherein said heterocycle is optionally fused to a phenyl ring;

- In claim 1, the definition of variable " R_{2a} " begins with the following:

"R_{2a} is a divalent C₃-C₄ alkylene which together with X and the carbon atom to which X and R_{2a} are"

Moving down five lines from this point, the following phrase occurs:

"R₁₂ and R_{12a} is a C₆ or C₁₀ aryl".

On the line following this, the following phrase is recited:

"R₁₂ and R_{12a} is Het".

These two phrases are objected to for grammatical reasons, i.e., the following phrase is grammatically incorrect: "R₁₂ and R_{12a} is".

The following is suggested instead: each of R₁₂ and R_{12a} is

- Each of claims 9-11 make reference to the side chains of certain D- or L- amino acids. However, the side chain of e.g., D-aspartic acid is entirely indistinguishable from the side chain of L-aspartic acid. Accordingly, if side chains are going to be recited, the stereochemistry becomes entirely superfluous. Applicants have responded to this by providing an analysis that one can find in any introductory organic chemistry textbook. However, applicants have completely missed the point being made by the examiner. To take a specific example, the **side chain** of L-aspartic acid is the following: -CH₂-COOH. As it happens, the side chain of D-aspartic acid is also the following: -CH₂-COOH. The group "-CH₂-COOH" is completely indistinguishable by any chemical or physical test from the group "-CH₂-COOH". Moreover, they are indistinguishable by any "semantic" test. They are one and the same. The "side chain" of an amino acid does not include the chiral center. One option for claim language (in the case of claim 9) would be the following:

The compound of formula I... wherein R₅... is the side chain of an amino acid selected from the group consisting of aspartic acid, glutamic acid, valine, and tert-butylglycine, and wherein the carbon bearing R₅ is of the D or L configuration.

- In claim 17, the meanings of the terms (e.g., "Tbg") are undefined.
- Claim 45 is rendered indefinite by recitation of the term "racemic mixture of diastereomers". As indicated previously, applicants could, in principle, claim any of the following:

45. A compound of formula Ib or a diastereomer or an optical isomer thereof...etc.

103. A mixture consisting of a compound according to claim 45, and at least one stereoisomer thereof.

104. The mixture according to claim 103 which consists of several diastereomers of a compound according to claim 45.

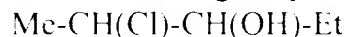
105. The mixture according to claim 104, wherein at least two of said diastereomers are racemates of one another.

106. The mixture according to claim 103, consisting of 100 stereoisomers of a compound according to claim 45, each of which is a racemate of another compound present in the mixture.

107. The mixture according to claim 106, wherein 50 pairs of racemates are present.

108. The mixture according to claim 107, wherein the molar ratio of each member of the pair is 1:1.

Consider the following simple compound, which is 2-chloro-3-hydroxypentane:



There are four isomers, i.e., the following:

- (1) 2R, 3S
- (2) 2R, 3R
- (3) 2S, 3S
- (4) 2S, 3R

Compound #1 is a diastereomer of compound #2, compound #2 is the enantiomer of compound #3, compound #3 is a diastereomer of compound #4, compound #1 is the enantiomer of compound #4, etc. Suppose that each of these four stereoisomers are present in solution in equal amounts. Is it applicants' position that this mixture would constitute "racemic mixture of diastereomers", and if so, which are the diastereomers? The term "diastereomer" is a relative one. One cannot simply have a vial which contains a diastereomer *per se*; of course, one can have a vial which contains a diastereomer of another stereoisomer. Thus, in this example, each one of the four compounds is a diastereomer of two other stereoisomers; there are no compounds in the mixture which are not diastereomers of at least one other compound. It thus becomes a question of bookkeeping and semantics. In applicants view, exactly which of these four compounds are the racemates, and which are the diastereomers? The term at issue does not make sense, and should be eliminated. (See also claims 59-60). In principle, applicants could claim the following, with further modification to reflect the 1:1 molar ratio between the first stereoisomer, and the enantiomer thereof, and to reflect the 1:1 molar ratio between the quantity of each of the diastereomers, and their enantiomers:

A mixture of stereoisomers comprising:

(a) a first stereoisomer, and the enantiomer thereof, in combination with (b) a mixture of diastereomers of said first stereoisomer, and the enantiomers of each of said diastereomers,

- In claim 75, the abbreviations "acca" and "Np" appear, but are undefined in the claim.
- In claim 75, one might infer that variable "P3" refers to the amino acid bearing R₃; however, this is not made clear.
- Claim 79 recites that the compound is "selected from the group consisting of" the indicated substituents. However, only one compound is defined; given the absence of any "choice", there is no "selection".
- In claim 77, the meanings of the terms (e.g., "Tbg") are undefined.
- In claim 78, the meanings of the terms (e.g., "Tbg") are undefined.
- In claim 79, the meanings of the terms (e.g., "Tbg") are undefined.

- In claim 80, the meanings of the term "Dnl" is undefined.
- In claim 106, the term "cleavable" renders the process indefinite as to whether cleavage takes place.
- Claim 106 recites that the carboxyl protecting group is an ester. The meaning of this is briefly described on p 41, line 22+. What is intended is not that the group "CPG" is itself an ester, but rather, that the substituent "CPG", taken together with the carbonyl group to which it is bonded, is an ester. Either of the following could be used:

The process.... wherein said carboxyl protecting group (CPG), taken together with the carbonyl group to which it is bonded is an ester, wherein said ester is one which is hydrolyzed by treatment of the ester with a mild reducing agent, or said ester is selected from the group consisting of an alkyl ester, an aralkyl ester, and an ester which is cleaved by mild base treatment.

The process.... wherein said carboxyl protecting group (CPG), taken together with the carbonyl group to which it is bonded, is an alkyl ester, an aralkyl ester, an ester which is cleaved by mild base treatment or an ester which is hydrolyzed by treatment with a mild reducing agent.

- The process claims (claims 103-106) are rendered indefinite by their failure to recite a step for isolation of the final product. At the end of the reaction cycle, one is left with a round-bottom flask which contains the target compound, together with solvent, some starting materials, and probably other impurities. A chemist who is in possession of such a mixture is not in possession of the final product. In principle, each of claims 103-106 could be drawn to a method of preparing a mixture which contains the target compound, but if the claims are going to be drawn to a process for preparing the compound of formula I *per se* (as opposed to a mixture which contains the compound), then the claims should recite a step for isolating the compound of formula I.
- In claim 114, the term "ribavirin" may be used if accompanied by the chemical name that this term represents.

- Claim 114 requires a component which is not required by claim 99. Accordingly, the propriety of claim dependence is called into question. It is suggested that claim 114 be redrafted so that it is dependent on claim 1, or else claim 99 should be amended to recite that ribavirin is optionally present.

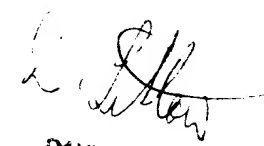
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No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.


DAVID LUKTON
PATENT EXAMINER
GROUP 1300